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Long-term trends in antithrombotic drug prescriptions among adults age 80 years and over from primary care. A temporal trends analysis using electronic health records

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Long-term trends in antithrombotic drug prescriptions among adults age 80 years and over from primary care. A temporal trends analysis using electronic health records

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Purpose: This study aimed to estimate trends in antithrombotic prescriptions from 2001 to 2015 among people aged 80 years and over within clinical indications.

Methods: A prospective cohort study with 215,559 participants registered with the UK Clinical Practice Research Datalink (CPRD) from 2001 to 2015 were included in the analyses. The prevalence and incidence of antiplatelet and anticoagulant drugs were estimated for each year, and by five clinical indications.

Results: The prevalence rate of antithrombotic prescriptions among patients over 80 years of age and diagnosed with atrial fibrillation increased from 53% in 2001 to 77% in 2015 (P_{trend} <0.001). Anticoagulant prescriptions rates also increased five-fold in older adults with atrial fibrillation from around 10% in 2001 to 46% in 2015 (P_{trend}<0.001). Clopidogrel prescribing rates in patients over 80 years of age and with venous thrombosis increased from 0.4% in 2001 to 10% in 2015 (P_{trend}<0.001). Warfarin prescribing in older patients with venous thrombosis increased from 13% in 2001 to 21% in 2015 (P_{trend}<0.001).

Conclusion: The use of antithrombotic drugs increased from 2001 to 2015 in people age 80 years and over across multiple clinical indications. Assessing the benefits and harms of antithrombotic drugs across different clinical indications in older people is a priority.

Key Words: anticoagulants; antiplatelets; elderly; prevention; primary care

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Ageing is associated with increased risk of cardiovascular diseases (CVD), including coronary heart disease (CHD), venous thromboembolism (VTE), atrial fibrillation (AF), peripheral arterial disease (PAD), and stroke. Antithrombotic therapies (ATT) (i.e. antiplatelet and anticoagulant drugs) have been shown to be effective at reducing the risk and/or recurrence of major CVD events in younger populations (< 80 years of age).(1-5) The use of ATT in patients over 80 years of age remains controversial, however, given their potential association with increased risk of bleeding.(2, 6-9) Valid data on the prevalence of anticoagulant and antiplatelet therapies among adults over 80 years of age in the presence of comorbidities and frailty is of major clinical relevance. Comorbidity and frailty are associated with polypharmacy,(10) and are important factors influencing the risk of potential complications (i.e. bleeding) associated with antithrombotic drugs in very old patients.(11, 12) The evidence about long-term trends in the prescription of antiplatelet and anticoagulant use in adults over 80 years of age is scarce and of varying standards (i.e. small samples, self-reports).(13) Reliable data on the use of ATT across different subgroups of very old patients is essential to inform clinical practice and for future planning of health care resources. The present study used a large primary care database to investigate patterns in the prescription of ATT drugs from 2001 to 2015 in patients aged 80 years and over. In particular, the study compared ATT prescriptions patterns across the main indications (e.g. AF, VTE, PAD, and major CVD) and patient characteristics (e.g. frailty, age).

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METHODS

Study Design

A prospective sequential cohort study was implemented in the UK Clinical Practice Research Datalink (CPRD), the world's largest database of primary care electronic health records, covering approximately 7% of the UK population.(14) The CPRD population is considered to be representative of the UK population, and includes comprehensive clinical, referral, and pharmacological data recorded in primary care, which have been validated in several studies.(15) Prescriptions are not directly linked to a clinical diagnosis in CPRD (may be linked to Read codes via a unique ID consultation number) and the study considered only prescriptions issued within the first 4 weeks as being likely to be related to the same condition.(16)

Study Participants

The sample was drawn from the April 2017 release of CPRD. Stratified sampling by age, sex, and study year was employed to ensure adequate representation of older ages. Eligible participants were selected from patients aged at least 80 years old and registered with the UK Clinical Practice Research Datalink (CPRD) at any time between 1st January 2001 and the 31st December 2015. The study excluded 2016 information because delays in practice data update by the CPRD could fail to capture recent data. For each calendar year from 2001 to 2015, and for each single year of age from 80 to 105 years, 1000 patients were sampled without replacement, from the population of patients registered during that year. This yielded a cohort of 215,599 patients whose primary care electronic health records were investigated. As per study protocol, the sample size was sufficient to estimate a proportion with precision (confidence interval width) of less than +/–1%.

Outcome measures

The main measures for the study were antiplatelet (e.g. aspirin, clopidogrel, dipyridamole, ticagrelor, prasugrel) and anticoagulant (e.g. warfarin, heparin, dabigatran, rivaroxaban, apixaban) drug prescriptions. Ticagrelor and prasugrel were available for analysis from 2012 onwards, while dabigatran and apixaban from 2010 onwards. Gemscript codes capturing drugs based on the British National Formulary (BNF) were used to identify antiplatelet and anticoagulant drugs prescribed during the study period, from 01/01/2001 to 31/12/2015. Only prescriptions who were co-prescribed on the same date of a relevant diagnosis (ie AF, DVT, PAD, CHD, CVS) or in the following 28 days were considered. Each outcome variable was constructed as a binary (yes/no) independent measure based on all relevant drugs available for prescription during the study period. An overall ATT outcome variable was developed reflecting either anticoagulant or antiplatelet drug prescriptions during the study period. To explore trends in most commonly prescribed ATT drugs, separate binary variables were developed for aspirin, clopidogrel, dipyridamole, ticagrelor, warfarin, heparin, and dabigatran. The study considered both oral and injectable ATTs to offer a more comprehensive understanding about prescription patterns over time.

Indication exposure

Read codes used by GPs to record a clinical diagnosis in primary care were used to develop specific binary variables (yes/no) representing common indications for ATT prescriptions including atrial fibrillation (AF), venous thromboembolism (VTE), peripheral arterial disease (PAD), cerebrovascular diseases (including, ischemic stroke and transient ischemic attack), and coronary heart disease (CHD) (e.g. myocardial infarction, angina). The validity and accuracy of Read medical codes have been documented extensively.(17-20)

Covariate measures

Characteristics known to be associated with variation in antithrombotic prescribing were selected and included gender, five-year age group, and frailty. Frailty status was assessed using a previously published 36-item electronic Frailty Index (eFI).(21) The eFI was constructed from the cumulative deficit frailty model with the eFI score calculated by the presence or absence of individual deficits as a proportion of the total possible.(22) Quantitative traits, including blood pressure, and polypharmacy were omitted from the eFI score for this study. Categories of fit, mild, moderate and severe frailty were defined following Clegg et al.(21) Gender was developed as a binary variable (men vs women), and based on their age at each sampling year, study participants were grouped into the following age categories: 80-84, 85-89, 90-94, 95-99, and 100 and over.

Statistical analysis

Descriptive statistics were used to calculate prevalence and inception rates for antiplatelet and anticoagulant drugs separately for each study year. The crude prevalence of ATT prescription was estimated by dividing the total number of ATT prescriptions recorded during each study calendar year by the total number of patients with a relevant clinical indication registered in CPRD during that calendar year. The number of ATT prescriptions was calculated for each calendar year of follow-up for each individual based on their clinical condition. Annual proportions were calculated for overall (e.g. ATT, AC, AP) and specific (e.g. aspirin, clopidogrel, ticagrelor, dipyridamole, warfarin, heparin, and dabigatran) drugs, stratified by the clinical indication (e.g, AF, PAD, DVT, CHD, CVS). Linear regression analyses were conducted to analyse trends in proportion by each clinical condition and the p-value for trend was calculated. Piecewise linear regression has been used to estimate a potential non-linear relationship between ATT prescriptions and time to identify any potential inflection points in

ATT prescribing trends. The crude incidence (inception) of ATT was estimated per 100-person years at risk for each clinical indication separately. Each patient contributed person-years from the start date for each calendar year (defined as latest of the 1st of January of each study sampling year (2001 to 2015), age 80 years, practice up-to-date standard, or start of the participant's record in the CPRD) to the end date (defined as the earliest of date of ATT prescription, date of death, the end of CPRD record, or the 31st of December of each calendar year). The incidence rate was estimated by totalling the number of patients with a first recording of ATT in each specific year, and then dividing this number by the total person years of follow-up for all patients during a specific year. The person-time denominator included all patients with the clinical indication of interest registered in CPRD during a specific calendar year whether or not they were prescribed an ATT medication. These estimations have been performed separately for overall and each specific prescription, stratified by clinical indication. For inception analyses, patients with a relevant (i.e. antiplatelet or anticoagulant) drug prescription anytime prior to 2001 or the year they turned 80 years of age were excluded. Drug prescriptions (not patients) issued before a condition diagnosis (e.g. atrial fibrillation, DVT, CHD) were excluded. A series of sensitivity analyses were performed to evaluate whether the trends in ATT proportions varying with patients age or frailty status within each clinical condition. The proportion of patients who were prescribed both AP and AC agents ranged from around 17% in 2001 to around 6% in 2014. For the present study purposes, however, these patients were analysed independently. The analysis was performed using STATA 14.

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RESULTS

Table 1 illustrates the characteristics of the study participants at selected years. The initial study sample included 215,559 participants aged at least 80 years at the time of sampling. The study included a greater proportion of women than men at each study year, with the proportion of participants age 85 to 94 years increasing over time. There was also a five-fold increase in the proportion of participants classified as severely frail between 2001 (3.7%) to 2015 (21.3%). The proportion of participants diagnosed with AF and DVT increased almost five-fold from 2001 (4.7% and, respectively, 2.2%) to 2015 (24% and, respectively, 11.2%).

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Table 1: Characteristics of participants for selected years of study. Figures are number and percentages.

		Year							
		2001		2005		2010		2015	
		N	%	N	%	N	%	N	%
Total		21155		56672		63359		55920	
Gender	Male	5931	28.0	17187	30.3	20388	32.2	19560	35.0
	Female	15224	72.0	36947	69.7	42971	67.8	36360	65.0
Age Group	80-84	4975	23.5	12523	23.8	12543	19.8	11262	20.1
	85-89	4957	23.4	16903	32.1	22359	35.3	18905	33.8
	90-94	4950	23.4	13541	25.7	17326	27.3	16195	29.0
	95-99	4666	22.1	7733	14.7	8986	14.2	7581	13.6
	100-105	1607	7.6	1972	3.7	2145	3.4	1977	3.5
Frailty	Fit	10914	51.9	16767	32.0	11469	18.3	7986	14.5
	Mild	6570	31.2	20329	38.9	22388	35.7	17607	32.0
	Moderate	2764	13.2	11254	21.5	18819	30.0	17750	32.2
	Severe	773	3.7	3952	7.6	10052	16.0	11720	21.3
Atrial fibrillation	Yes	1042	4.7	4707	8.3	9424	14.9	13438	24.0
Deep vein thrombosis	Yes	469	2.2	2181	3.8	4501	7.1	6361	11.4
Peripheral artery disease	Yes	514	2.4	2121	3.7	4187	6.6	5806	10.4
Cerebrovascular disease	Yes	1902	9.0	6954	12.3	12662	20.0	17255	30.9
Coronary heart disease	Yes	2083	9.8	8038	14.2	15232	24.0	21094	37.7

Figure 1 illustrates prevalence for overall ATT prescriptions over the study period for each of the five clinical subgroups. The general trend was for a steady increase in ATT, OACs, and antiplatelet prescriptions across all five clinical conditions. For instance, ATT prescriptions in AF increased significantly from 53% in 2001 to around 78% in 2015 (P_{trend} <0.001). The sharpest increased in AF was observed with regards to OAC prescribing, from 10% in 2001 to 46% in 2015 (p-trend<0.001). Concerning antiplatelet prescriptions in AF, there was a gradual increase in prevalence rates from 2001 (45%) to 2012 (55%) (P_{trend} <0.001), followed by a non-significant decline to 2015 (37%) (P_{trend} =0.118). Within CHD, cerebrovascular diseases, and PAD conditions an increasing trend emerged across all ATT prescriptions. Supplementary data (Figure S1) illustrates an increasing trend in inception rates across all ATT prescriptions within each clinical condition, being more pronounced for OACs prescribing in AF and DVT conditions.

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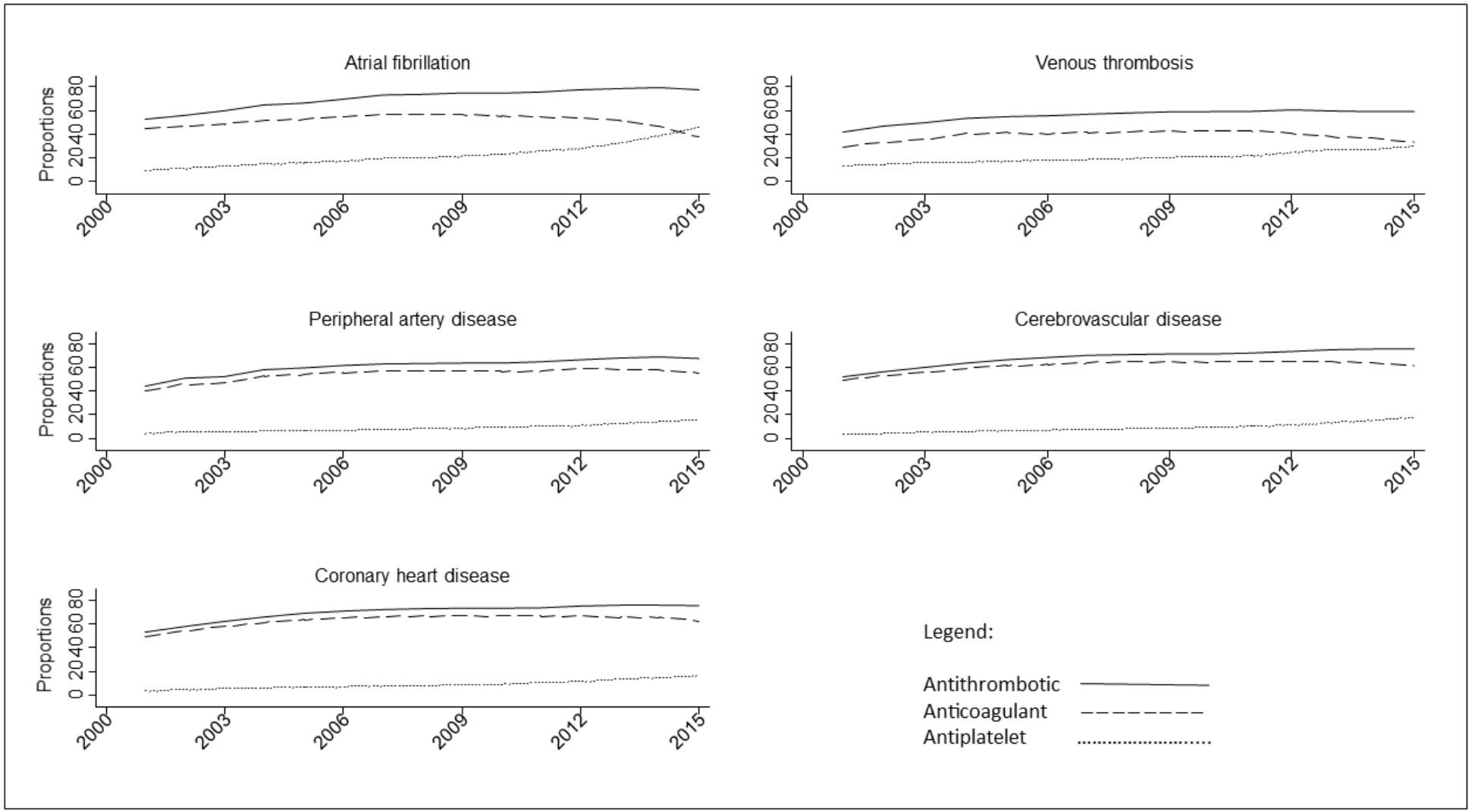

Figure 1 Trends in overall antithrombotic prevalence rates by clinical indication.

Analyses stratified by the most commonly prescribed antiplatelet drugs (Figure 2), indicated increasing trends in clopidogrel and ticagrelor prescriptions throughout the study period. For instance, the prevalence of clopidogrel prescribing in PAD, increased from 2% in 2001 to 16% in 2015 (P_{trend} <0.001). Aspirin prescribing in PAD revealed a non-linear trend, with prescription prevalence increasing from 39% in 2001 to 51% in 2012 (P_{trend} <0.001), followed by a non-significant decline to around 43% in 2015 (P_{trend}=0.117). Similar trends were observed across other clinical conditions. Notably the sharp increase in clopidogrel prescribing from around 2010 within cerebrovascular disease condition, with prevalence increasing threefold (P_{trend} <0.001) from 2010 (11%) to 2015 (28%). The spline related to clopidogrel prescribing in AF indicated an inflection point around mid-2009, after which the prescription rate increased to 2012. For aspirin prescribing in AF, the inflection point was observed in 2012, after which annual prescription rates declined at a steady rate to 2015. A similar trend was observed for dipyridamole prescribing in AF, with an earlier inflection point around mid-2009 followed by decline to 2015. Similar findings emerged with regards to the rest of clinical conditions (data not presented here). Inception (incidence) rates results (Supplementary Figure S2), revealed a rather stable trend in aspirin prescribing to around 2012 across most clinical conditions (2009 within CHD), followed by a declining trend over the past three-years of the follow-up. Clopidogrel prescribing, by contrast, showed a linear increasing trend in inception rates with a sharp increase from 2011 (11%) to 2015 (63%).

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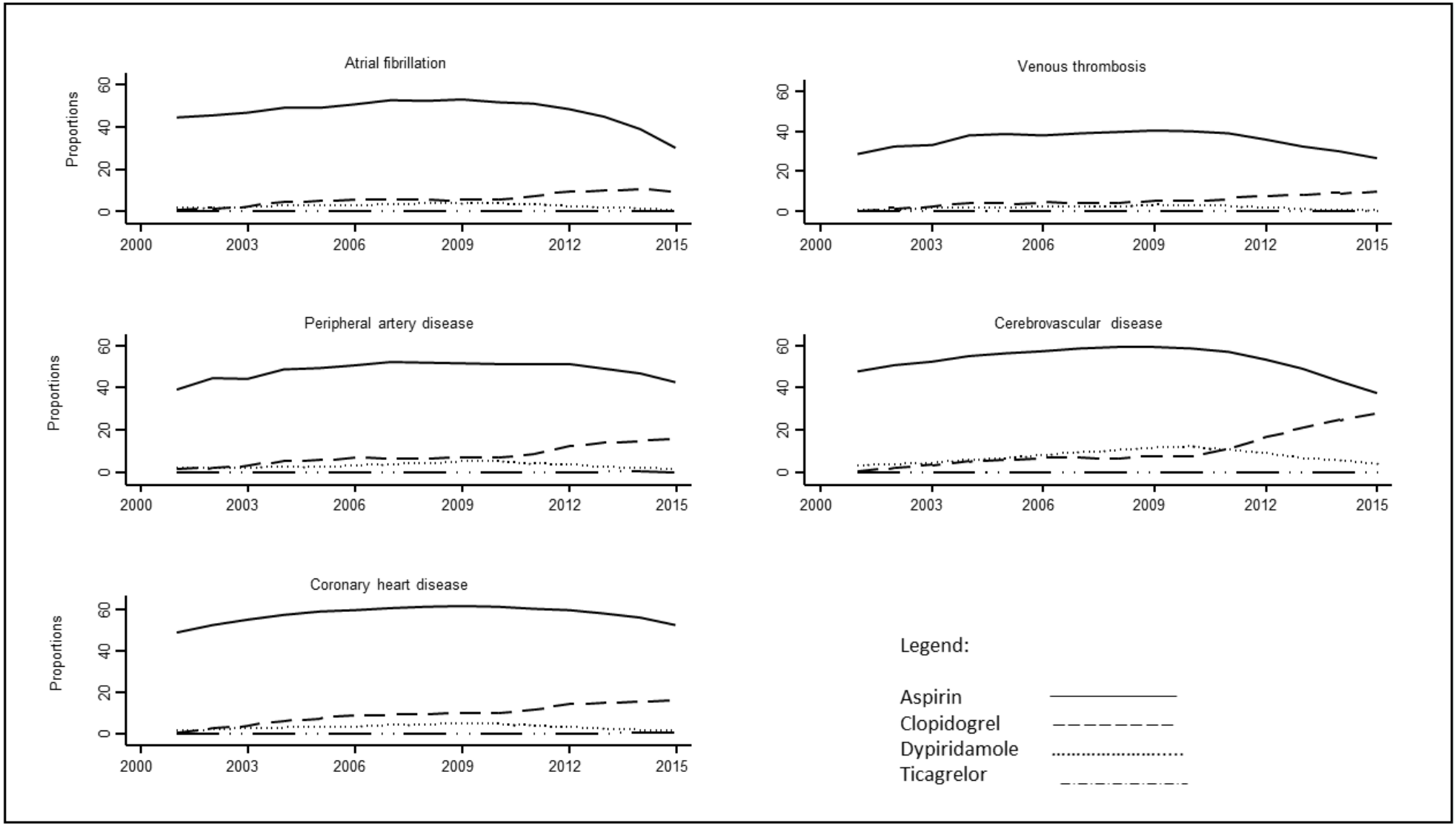

Figure 2 Trends in specific antiplatelet drugs prevalence rates by clinical indication.

Anticoagulant-specific analyses (Figure 3) documented an increasing in trend in the prescription of warfarin, heparin and dabigatran within all clinical conditions. The highest prescription was observed among patients diagnosed with atrial fibrillation and DVT conditions, with the former showing the steepest increase. For instance, the prescription of warfarin in atrial fibrillation increased from 4% in 2001 to 12% in 2016 (P_{trend}<0.001). Dabigatran prescription rates in atrial fibrillation presented the largest increment from around 0.2% in 2012 to 2% in 2015 (P_{trend} <0.001). The spline related to dabigatran prescribing in DVT indicated an inflection point around the beginning of 2012, after which the prescription rate continued to increase at a modest rate to 2015. For heparin prescribing in DVT, the inflection point was observed towards the end of 2012, after which annual prescription rates declined to 2015. Of note, the inflection point for heparin prescribing in AF was observed around mid-2009, followed by an increasing prescription rate to 2015. There was no evidence for a non-linear trend with regards to warfarin or heparin prescribing in other conditions (data not presented here). Regarding inception (incidence) rates, the overall trend was for increased prescribing rates across the study period within each clinical condition and for all three OACs (Supplementary Figure S3).

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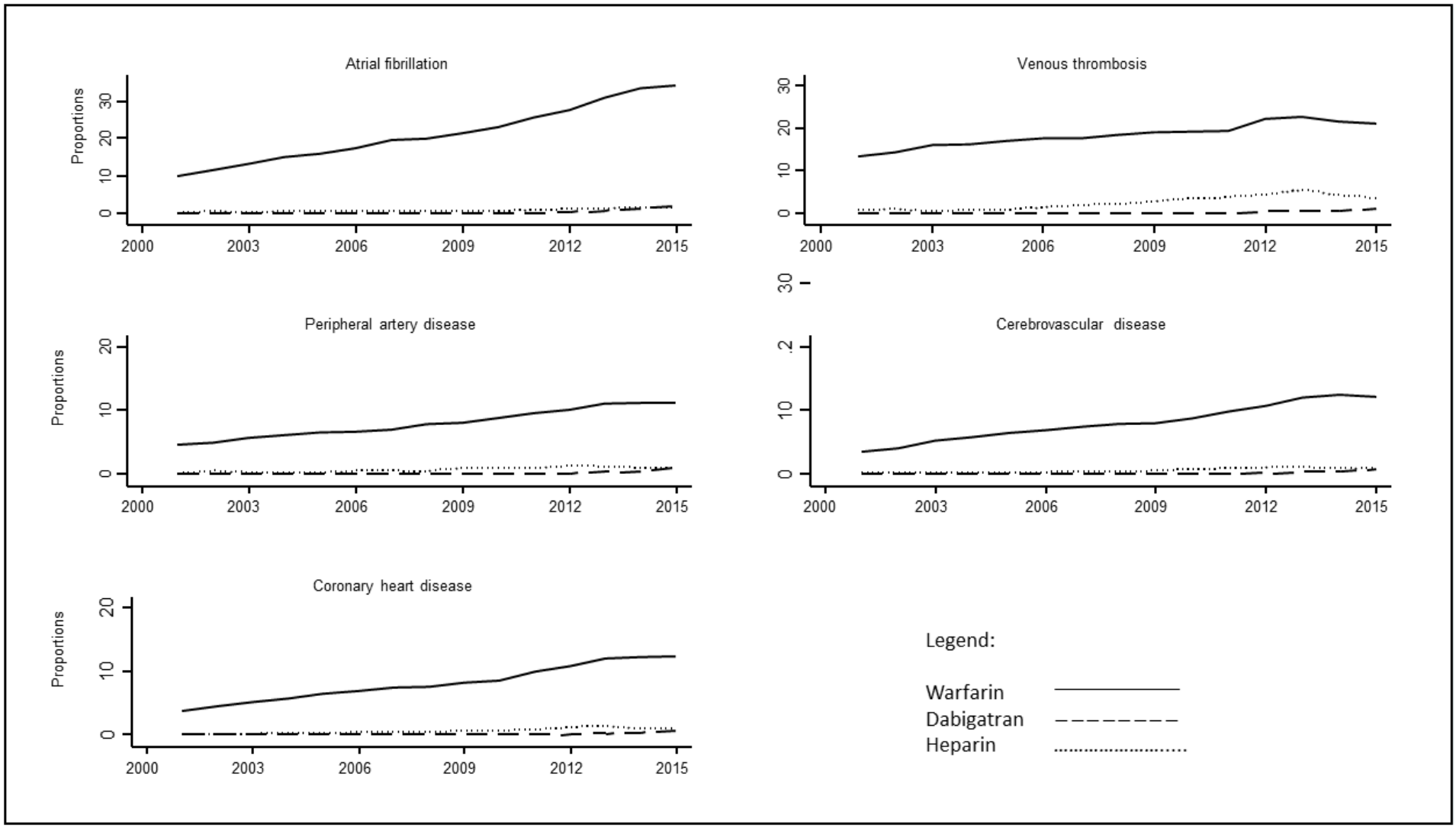

Figure 3 Trends in specific anticoagulant drugs prevalence rates by clinical indication.

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Sensitivity analyses

The results of sensitivity analyses revealed a general increasing trend in ATT prescribing across all age groups within atrial fibrillation, CHD (except antiplatelet prescribing in those 100 years of age and older), and cerebrovascular disease conditions (Supplementary Figure S4, PAD results available on request). Regarding DVT and PAD conditions, antiplatelet prescription rates tended to increase among the younger age groups (80 to 89 years), appeared stable in those age 90 to 95 years, and tended to decline among those aged 95 years of age and over. Frailty-specific analyses Supplementary Figure S5, PAD results available on request), revealed a consistently increasing trend in OAC and antiplatelet prescribing rates across all frailty groups and within each clinical condition. The highest prescription rates were observed among patients within the highest quartile of frailty.

DISCUSSION

Using routinely collected primary care data, the prescription of ATT for patients over 80 years of age diagnosed with specific clinical indications increased significantly from 2001 to 2015. The most consistent increase was observed with regards to anticoagulant drugs in patients diagnosed with AF, with the prevalence rates increasing five-fold between 2001 and 2015. Regarding, antiplatelet prescribing the largest increase was observed among patients diagnosed with PAD, which presented with a 33% increment in prevalence rates during the 15-years follow-up. Aspirin (sold over the counter in the UK since 1915) was the most commonly prescribed specific antiplatelet drug, with warfarin being the most commonly prescribed anticoagulant drug within each clinical indication. Notably, over the last five years of the study clopidogrel prescribing increased steeply, while aspirin showed a modest decline. These trends were observed across all clinical indications. With regards to anticoagulants drugs, dabigatran revealed the most consistent and steepest increment in prescribing rate since their introduction around 2011. Across all clinical conditions, an inflection point for clopidogrel was observed around mid-2009, after which the rate increased significantly to 2015. A similar trend was observed for dabigatran, but the

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inflection point was towards the beginning of 2012. For aspirin prescribing, the inflection point was observed around beginning of 2012, after which the prescription rate declined to 2015. Sensitivity analyses by frailty status and age revealed higher ATT prevalence rates within the most frail subgroup and among the youngest old (80 to 89 years of age). The increased ATT prescribing among the most frail older participants is possibly expected, considering that polypharmacy is over two times more common among the frail older adults compared to their more robust older peers.(23) Because of their reduced resilience, frail older adults are at greater risk of adverse drug effects, including falls, fractures, and death.(24) For instance, the risk of death was suggested to increase by 22% with each additional drug prescribed in frail older men previously defined as robust.(25) It is, therefore, important to consider the frailty status of very old patients when prescribing ATT and to monitor frequently for their net benefits and net harms. The benefits of ATT need to be considered in the context of comorbidity, drug interactions, and goals of care.

Inception rates also presented an upward prescribing trend, suggesting increased incidence of anticoagulants and antiplatelet prescribing among patients age 80 years and over diagnosed with specific clinical conditions. Antiplatelet inception rates appeared to decline during the last two years of study follow-up, and since CPRD capture medications prescribed at the time of the patient interaction this decline may reflect the availability of over-the-counter purchase of aspirin. Notably, the decline in aspirin inception rates seems to coincide with an increment in clopidogrel inception rates, suggesting that clinicians may favour the latter given evidence for the clinical and safety superiority of clopidogrel to aspirin in some clinical conditions (e.g. PAD, CHD).(26, 27) In 2011, the American Heart Association (AHA) (28) recommended clopidogrel use among patients diagnosed with ischemic stroke that were allergic to aspirin. Similarly, in 2014 NICE recommended that aspirin prescription should be replaced with an anticoagulant (e.g. dabigatran) among patients with AF.(29) Such changes in clinical guidelines may have affected aspirin and clopidogrel prescription patterns recently. Patent expiry for clopidogrel expired in the UK in 2012, and this may also account for the increased clopidogrel prescription rate in the

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later part of the study period because of the reduced costs to the NHS. Concerning anticoagulants drugs, the inception rates increased gradually for warfarin, heparin and dabigatran. There was, however, a decline in inception rates for warfarin and heparin drugs from around 2012-2013, which appears to coincide with the change in NICE recommendations for the use of dabigatran as the first line option for stroke prevention in AF among patients aged 75 years or over. (30) The release of several QoF and NICE guidelines during the study period may have improved the capture of many of the medical conditions that contributed to the Frailty Index. Thus, it is possible that the 5-fold increase over the study period in the proportion of patients identified as frail may be in part due to improved recording of medical information by GPs.

Antithrombotic prescribing in very old patients has gain increased interest over the recent years. Yuan et al.(31) suggested that around 75% of participants (mean age 76 years) diagnosed with CVD received at least one antithrombotic drug in the THIN database during 2000 and 2006, and this study found similar rates in older patients and in more recent years. Kantor et al. (10) using NHANES cross-sectional data found an increasing trend in warfarin use from 1.3% in 1999-2000 to 1.8% in 2009/2010, followed by a decline to 1.5% in 2011-2012. Our study with longitudinal data documented higher prevalence rates of warfarin prescribing in older patients and across multiple clinical indications. Cheng et al.(32) indicated that around 11% of stroke survivors in the US self-reported anticoagulant prescriptions between 2000 and 2006. The present study using routinely collected primary care data, reported similar trends and further indicated superior rates (20%) in recent years among older patients with multiple cerebrovascular events (e.g. ischemic stroke and TIA). Cheng et al. also found that around 57% of their participants reported the use of aspirin for secondary CVD prevention, which is substantively lower than the 70% rate observed in this study. This difference is possibly due to the older age of the present study population, as well as, increasing rates of ATT prescribing over the recent years.

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The present study represents one of the first primary-care based investigations to estimate longitudinal trends in the prescription of traditional and novel ATTs across multiple clinical conditions exclusively among patients aged 80 years and over. Specific strengths of the study include a comprehensive description of antithrombotic drugs prescription in people age 80 years, long-term follow-up period, consideration of multiple clinical indications, and the use of routinely collected prospective data. Drug prescriptions and clinical diagnoses were based on clinical records increasing the reliability and validity of the study findings. As with most observational studies, there are several limitations. The study data was restricted to participants aged 80 years and over and may not apply to younger age groups or to those with other clinical indications than those considered here. We deliberately selected very old patients as this group is the fastest growing segment of the UK population and with limited evidence about the patterns of ATT prescriptions. The distribution of men and women over the study period may also reflect survival bias (women tend to outlive men in older ages). Also, the study did not directly estimate the proportion of participants that should have been prescribed ATT or those who were inappropriately prescribed ATT. These are important questions that deserve more detailed discussion that would have been possible within the constraints of the present study. The study data may have underestimated the prevalence and incidence rate of aspirin prescribing as these drugs are also available over-the-counter. The study sampling strategy may have also introduced a certain degree of bias (e.g. incomplete list of all eligible patients, oversampling) that may have resulted in underestimation or overestimation of true prevalence and incidence estimates. However, the study findings are comparable to those generated by other longitudinal studies(31) and we used similar methodology in our previous research with the CPRD.(33)

In summary, the prescription of antithrombotic drugs among adults over 80 years of age in the primary care has increased consistently from 2001 to 2015 across multiple clinical indications. The increased prescribing rates of ATTs over time may be due to several factors, including a growing body of evidence supporting the effectiveness of ATT in secondary prevention of major CVD events, the introduction of

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safer ATTs over the recent years (e.g. dabigatran), increased life expectancy in patients with diverse CVD symptoms, or a combination of all these factors. Future studies are needed to evaluate whether increased use of novel anticoagulants and clopidogrel in recent years corroborate with a reduction in incidence of major CVD events and adverse acute events (e.g. bleeding, functional disability). Additional research is also necessary to identify the proportion of patients aged 80 years or over that could benefit from ATT and failed to receive the therapy,(34, 35) as well as those with a contra-indication for ATT that received the therapy.(36, 37) It may be that contra-indication for ATT prescribing in elderly is higher soon after a drug approval and that it may decline after ATT drugs were on the marker for one or more years. (38)

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Conflict of interest: The Authors declare that there is no conflict of interest.

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